

UNDERSTANDING THE DISEASE



Ten tips on sepsis-induced thrombocytopenia

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Thrombocytopenia is a commonly observed phenomenon in sepsis and a frequent cause of anxiety for the clinician at the bedside, raising a host of questions, including the concerns about a low platelet count, the interaction between sepsis and platelets, the other causes of thrombocytopenia, or the indications of platelet transfusion. Though much of the effect of sepsis on platelet physiology and function is yet unknown, in this article we have undertaken to address many of these common questions.

How do we measure platelets?

A platelet count is the number of platelets per volume, typically analysed by automated instruments. In cases of abnormal counts, counts are repeated manually. Reported platelet counts are strictly quantitative and qualitative platelet dysfunction can occur in patients with low, normal or elevated platelet counts [1]. Platelet function can be affected by drugs, intrinsic platelet dysfunction, or renal or liver disease, and unfriendly environments. Specialised assays to measure platelet function exist and viscoelastic testing can provide some qualitative insights but their clinical relevance is controversial.

Thrombocytopenia is common in sepsis and is associated with outcomes

Thrombocytopenia (a platelet count $< 150,000/\mu\text{L}$) is common in intensive care unit (ICU) patients [2] and seen in $> 55\%$ of sepsis cases and at higher rates in septic shock [3, 4]. Severe thrombocytopenia ($\leq 50,000/\mu\text{L}$) [2]

develops in $\sim 30\%$ of thrombocytopenic septic patients [5].

Thrombocytopenia in sepsis is associated with worse outcomes [3] and, if early (< 24 h) or sustained, has prognostic utility [3, 4, 6]. However, it remains unclear whether thrombocytopenia in sepsis is an indicator (an affected “innocent bystander”) or cause (an “active participant” in organ injury) of sepsis severity [7]. The risk of coagulation-related complications increases at $< 100,000/\mu\text{L}$, and fear of bleeding complications may prevent clinicians from performing needed procedures or surgery.

Immune mechanisms connect sepsis to thrombocytopenia

Platelets are key players in haemostasis but also have crucial roles in inflammation. Immune-mediated platelet activation is an integral infection response, as platelets interact with immune and complement systems, releasing agents that promote neutrophil activation and leukocyte recruitment, express pattern recognition receptors, and stimulate neutrophil extracellular trap formation [8]. Severe thrombocytopenia is associated with dysregulated host immunity in septic patients with altered gene expression, including reduced leukocyte adhesion and increased complement signalling [7].

Vascular integrity—a link between thrombocytopenia and organ injury

Platelets safeguard vascular integrity by optimising the barrier function of microvessels and reducing extravasation of both water and plasma proteins, especially in inflammatory states. Platelets directly block gaps in the vascular lining, thereby maintaining endothelial structure, and release soluble factors that enhance endothelial barrier function. The loss of endothelium-supporting functions contributes to organ oedema and tissue haemorrhage in sepsis-induced thrombocytopenia [9].

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Differential diagnoses—sepsis-induced vs. other causes?

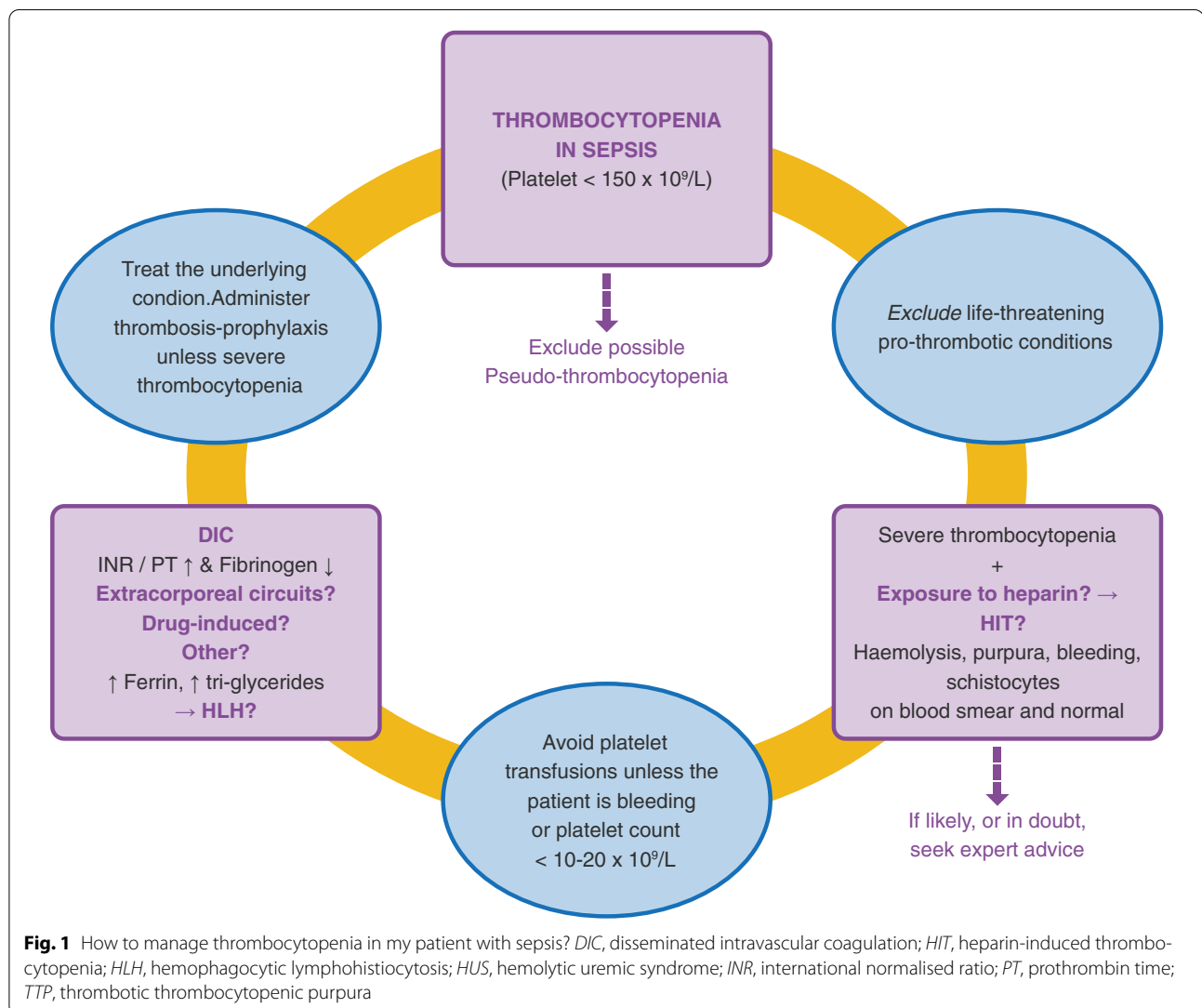
Sepsis-induced thrombocytopenia is a multifactorial phenomenon, as platelets are irreversibly expended in the immune response. Other aetiologies include entities such as disseminated intravascular coagulation (DIC) and sepsis-associated reactive hemophagocytosis [6]. However, while sepsis is a more common cause of thrombocytopenia, potentially lethal prothrombotic conditions should always be ruled out. These conditions include heparin-induced thrombocytopenia (HIT), immune-mediated thrombotic thrombocytopenic purpura (iTTP) and haemolytic uremic syndrome (HUS) (Fig. 1). Additional causes include drug-induced thrombocytopenia, immune thrombocytopenia (ITP), haemodilution, pseudo-thrombocytopenia (an in vitro phenomenon

caused by ethylenediamine tetraacetic acid (EDTA) that can be resolved by the use of citrated sample tubes), extracorporeal devices, and underlying hepatosplenic disease, malignancy or myeloproliferative disorders [10].

A review of the peripheral blood film (“smear”) can be useful in establishing the aetiology of thrombocytopenia, as can bone marrow aspiration in selected circumstances.

Antimicrobials can cause thrombocytopenia

Drug-induced thrombocytopenia, including that caused by antimicrobials (e.g.: vancomycin, antifungals, linezolid, beta-lactams, ciprofloxacin [11]) is responsible for 10–20% of ICU thrombocytopenia cases, and should be considered in severe thrombocytopenia ($< 20,000/\mu\text{L}$) complicated by bleeding, occurring 5–10 days after drug exposure. Stopping the drug (if feasible) is recommended,



and, in cases of severe bleeding, administering platelets, intravenous immunoglobulin (IVIg) ± corticosteroids [12].

Sepsis-associated coagulation activation and DIC are not the same

In sepsis, immune and coagulation systems are activated [7]. The coagulation response in sepsis is a continuum, and DIC represents one extreme, where the coagulation response is overwhelming and injurious. Despite wide-spread coagulation, bleeding, typically oozing from injection sites and wounds, is often seen in DIC. There is no specific treatment for DIC beyond effectively treating the precipitating cause, monitoring coagulation status, administering thromboprophylaxis (at a minimum) when possible and managing bleeding or thrombotic complications.

Thrombocytopenia in sepsis does not necessarily equal DIC. If in doubt, the International Society on Thrombosis and Haemostasis (ISTH) DIC score may be helpful (Fig. 1).

Risk of bleeding depends on more than just platelet count

Several studies have found higher rates of bleeding, often severe, in patients with thrombocytopenia [3, 4]. While severe thrombocytopenia is associated with bleeding, the correlation with platelet nadir is not always linear, suggesting that bleeding risk is not solely dependent on platelet count but rather due to alternative mechanisms such as endothelial dysfunction [4], e.g.: septic haematological ICU patients reported a higher incidence and severity of bleeding than non-ICU haematology patients with similar thrombocytopenia [13].

Thrombocytopenia does not exclude thrombosis

Sepsis is a risk factor for thrombosis even in thrombocytopenic patients—in one study, 4.5% of patients without thrombocytopenia developed new thrombi versus 7.5% of patients with thrombocytopenia [3]. Another study of haematological malignancy patients found that while thrombocytopenia $\leq 50,000/\mu\text{L}$ was generally associated with lower thrombosis incidence, the risk was increased in ICU patients [14]. It remains uncertain whether thromboprophylaxis use in thrombocytopenic patients reduces thrombosis risk.

Platelet transfusions have variable effects

While an appealing intervention, transfusion carries risks and is often inefficient at increasing platelet counts, therefore, transfusion is not recommended unless bleeding is present or thrombocytopenia is severe. Increased

mortality rates in sepsis patients receiving platelet transfusions is reported, though causality is unclear [15].

Conversely, a trial of prophylactic platelet transfusion for central venous catheter (CVC) placement found differences in catheter-related bleeding, suggesting some benefit to transfusion [16]. Current guidelines suggest transfusion to achieve platelet counts $>20,000/\mu\text{L}$ prior to CVC placement and other low-risk procedures, and counts $>50,000/\mu\text{L}$ prior to lumbar puncture and higher-risk procedures.

Take-home message

Thrombocytopenia in sepsis is common, but many uncertainties remain. Associations between thrombocytopenia and bleeding, transfusion, and mortality follow a “dose–response” pattern with worse outcomes accompanying more severe thrombocytopenia, but causality is not established.

Advances are required to better understand, and provide optimal support for, septic patients with thrombocytopenia.

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Declarations

Conflicts of interest

ML served as speaker for Shionogi and consultant for AOP Pharma and Viatrix. NDN serves on advisory boards for Inotrem and Adrenomed. LR has no conflict of interest to disclose.

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